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The specification has been amended to define number 38 as a "venous pressure gauge" in view of the examiner's concern

With respect to a kit being objected to as lacking a figure, hundreds of issued patents claiming kits do not include drawings of such kits. The undersigned is aware of no legal basis for such a requirement, nor how all of these patents could have issued in the absence of such figures if it is a requirement. However, these claims have been cancelled to facilitate prosecution.

Rejections under 35 U.S.C. 112

Claim 11 was rejected under 35 U.S.C. 112, as not enabled. This rejection is traversed on the basis that a number of vaccines are used to treat cancer and other disease, the most common being the BCG vaccine used for at least two decades. However, to facilitate prosecution this claim has been cancelled.

Claims 9, 10, and 16-19 were rejected under 35 U.S.C. 112, first paragraph, stating that there is no support in the application for the claims as originally. This rejection is traversed.

First, the claims as originally filed form part of the disclosure. This fact has long been recognized.

Second, the written description requirement does not mean that the claimed subject matter must have been actually reduced to practice. It is sufficient if it is described in sufficient detail for one skilled in the art to make and use that which is disclosed, as required under the enablement portion of the 35 U.S.C. 112. This applicant has done. Applicant has clearly specified at pages 11-12 that removal of soluble tissue necrosis factor receptor and other soluble cytokines can be removed to induce an immune response. At page 12, lines 1-16, applicant describes removal of these soluble cytokine factors (all of which were known in the prior art to

exist, although it was not known that there selective removal could be used to treat cancer or disease). Removal using an antibody column is specifically recited. Removal by immobilization of antibodies on ultrapheresis membrane filters is specifically recited. Moreover, by including the rejected claims in the application as of the date of filing, applicant demonstrated that he not only had described the claimed subject matter, but that he recognized it as part of his invention.

The most recent decision regarding written description was articulated by the Court of Appeals for the Federal Circuit in Amgen (Fed. Cir. January 6, 2003). They stated in relevant part:

" The purpose of the written description requirement is to prevent an applicant from later asserting that he invented that which he did not; the applicant for a patent is therefore required to "recount his invention in such detail that his future claims can be determined to be encompassed within his original creation." Id. at 1561, 19 USPQ2d at 1115 (citation omitted). Satisfaction of this requirement is measured by the understanding of the ordinarily skilled artisan. Lockwood v. Am. Airlines, Inc., 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997) ("The description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). We held in Eli Lilly that the adequate description of claimed DNA requires a precise definition of the DNA sequence itself -- not merely a recitation of its function or a reference to a potential method for isolating it. 119 F.3d at 1566-67, 43 USPQ2d at 1406 (holding the disclosure of the cDNA sequence of the insulin gene of a rat did not adequately describe the cDNA sequence of the insulin gene of every vertebrate). More recently, in Enzo Biochem, we clarified that Eli Lilly did not hold that all functional descriptions of genetic material necessarily fail as a matter of law to meet the written description requirement; rather, the requirement may be satisfied if in the knowledge of the art the disclosed function is

sufficiently correlated to a particular, known structure. See Enzo Biochem, 296 F.3d at 1324, 63 USPQ2d at 1613. **Both Eli Lilly and Enzo Biochem are inapposite to this case because the claim terms at issue here are not new or unknown biological materials that ordinarily skilled artisans would easily miscomprehend."** (emphasis added)

In summary, the issue is whether one skilled in the art would know that the applicant has invented what is being claimed, using the ordinary person in the art. The ordinary person in this art knew that antibodies had been bound to Sepharose or membranes since at least as early as the mid-1970's; that soluble cytokines such as TNFR1 and TNFR2 had been described in the literature for several years preceeding the filing of this application; and that applicant had tested a plasmapheresis system in clinical trials and shown that humans exhibited a significant reduction in tumor mass and inflammation, in the case of a multiple sclerosis patient. Therefore one skilled in the art would have known, based on page 12 and the claimed subject matter, that the applicant had described his invention in writing.

Claims 21 and 22 have been cancelled, mooting this rejection.

Rejections under 35 U.S.C. 102(b) or 103

Claims 1-4, 12, 14 and 20 were rejected under 35 U.S.C. 102(b) as anticipated by Lentz (1988) or U.S. Patent No. 4,708,713 to Lentz. Claims 5, 11, 13-15, and 21 were rejected under 35 U.S.C. 103 as obvious over '713 to Lentz. Claims 7, 8, 16 and 17 were rejected under 35 U.S.C. 103(a) as obvious over '713 to Lentz, in view of Chen, et al., J. Neuropathology and Experimental Neurology 56(5):541-550 (1997). Claims 5, 6, and 22-29 were rejected over Lentz in view of U.S. patent No. 5,861,483 to Wolpe. These rejections are respectfully traversed if applied to the amended claims. Claims 21-29 have been cancelled.

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The claims have been amended to incorporate the limitations of claim 7. Since claim 7 discloses selective removal of soluble cytokines, which is not disclosed by Lentz, claim 1 and claims dependent thereon are not disclosed by Lentz (1988) or '713.

Chen does not disclose that soluble cytokines such as sTNFR1 or sTNFR2 can be removed and that is sufficient to elicit an immune response that will result in killing of the tumor. Lentz teaches that if one removes every protein in the plasma having a molecular weight of about 48,000 (albumin) or larger, tumor reduction will occur. The test under 103 is whether one skilled in the art would be led, by the reference, to combine the references, as applicant has done, with a reasonable expectation of success.

There is simply nothing in these references that leads one to that conclusion. The result is simply too unpredictable. Applicant has now conducted numerous trials in humans with a variety of different cancers, and shown that selective removal of soluble cytokines such as sTNFR1 and sTNFR2 does result in an inflammatory response resulting in substantial decrease in tumor volume. This is enhanced by treatment with other types of therapy, including chemotherapy, hyperthermia, and radiation.

The prior art, in combination, says that one should remove ***many proteins, including soluble cytokines*** (which are of a lower molecular weight than albumin) if one wants to treat tumors. Chen provides no indication that removal of sTNFRs will result in reduction in tumor size. There is no correlation between "helping to evade an immune response" and something being solely responsible for preventing an immune response. Therefore Lentz in combination with Chen cannot make obvious the claimed subject matter.

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As the examiner has noted, U.S. Patent No. 6,379,708 to Howell, which is an issued U.S. patent, discloses and claims the same subject matter. Howell was filed ***after*** the priority date of this application.

Double patenting Rejections

The double patenting rejections are believed to be mooted in view of the amendments to the claims. As the examiner is aware, a double patenting rejection must be based solely on the claims, not in view of the specification. Nothing in the claims in U.S. Patent No. 6,231,536 or U.S.S.N. 09/083,307 makes obvious the subject matter of the claims as now pending, for the reasons discussed above with respect to the rejection under 35 U.S.C. 103.

Allowance of all claims as amended is earnestly solicited.

Respectfully submitted,

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APPENDIX: Marked up copy of Claims as amended

Sub C1 B1

1. (amended) A method for inducing an immune response against transformed, infected or diseased tissue comprising

[removing only components present in the blood having a molecular weight of 120,000 daltons or less,] selectively removing soluble cytokine receptor molecules until the transformed, infected, or diseased tissue is reduced in amount.

2. The method of claim 1 wherein the tissue is a solid tumor.

3. The method of claim 1 wherein the components are removed from one blood volume.

4. The method of claim 1 wherein the components are removed in multiple treatments.

5. The method of claim 1 further comprising treating the tissue with an agent selected from the group consisting of anti-angiogenic compounds, procoagulant compounds, cytokines, chemotherapeutic agents, and radiation.

6. The method of claim 5 wherein the agent is a cytokine and the cytokine is selected from the group consisting of GM-CSF, erythropoietin, thrombopoetin, G-CSF, M-CSF and SCF.

Please cancel claim 7.

8. (amended) The method of claim [7] 1 wherein the soluble cytokine receptor molecules are selected from the group consisting of soluble tissue necrosis factor receptor-1 ("sTNFR-1"), soluble tissue necrosis factor receptor-2 ("sTNFR-2"), soluble interleukin-2 receptor ("sIL-2R"), soluble interleukin-1 receptor ("sIL-1R"), soluble interleukin-6 receptor ("sIL-6R"), and soluble interferon-gamma receptor ("sIFN-gammaR").

9. The method of claim 8 wherein the cytokine receptor molecules are removed by binding to the cytokine or to an antibody or antibody fragment immunoreactive with the cytokine receptor molecules.

10. The method of claim 9 wherein the cytokine or antibody or antibody fragments are immolibized in a filter or column through which the patient's blood or plasma is circulated prior to being returned to the patient.

Please cancel claims 11.

12. (amended) A system for inducing an immune response against transformed, infected or diseased tissue comprising

a device for [removing only components present in the blood having a molecular weight of 120,000 daltons or less] selectively removing soluble cytokine receptor molecules, having inlet and outlet means for connection to a pump and tubing to recirculate the blood of a patient through the device.

Please cancel claims 13-15.

16. The system of claim 12 wherein the device is an absorbant colum selectively removing specific cytokine or cellular inhibitors from the blood.

17. The system of claim 16 wherein the cytokine or cellular inhibitors are selected from the group consisting of soluble tissue necrosis factor receptor-1 ("sTNFR-1"), soluble tissue necrosis factor receptor-2 ("sTNFR-2"), soluble interleukin-2 receptor ("sIL-2R"), soluble interleukin-1 receptor ("sIL-1R"), soluble interleukin-6 receptor ("sIL-6R"), and soluble interferon-gamma receptor ("sIFN-gammaR").

18. The system of claim 17 comprising cytokines or antibody or antibody fragments immunoreactive with the cytokine receptor molecules.

19. The system of claim 18 wherein the cytokine or antibody or antibody fragments are immobilized in a filter or column through which the patient's blood or plasma is circulated prior to being returned to the patient.

Sub C'

B1 cancelled

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20. The system of claim 12 wherein the blood is plasma.

Please cancel claims 21-29.

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APPENDIX: Marked up pages of specification and drawings as amended

approximately 7% of the total body weight) is processed over a period of approximately 2 ½ hours. The filtrate is then returned from the filtration device to the patient at the second site. Standard microprocessor controls can be used to regulate the blood flow, for example, by monitoring the volume of the blood products being removed, in combination with flow rate monitors and pump speed.

The entire system should first be flushed with saline and then treated with an anticoagulant or anticlotting agent, such as sodium heparin, to be sure that there are no locations within the system where blood clotting can occur. Moreover, small amounts of anticoagulants should be continually introduced into the blood stream directed to the ultrafilter to ensure than no clotting occurs during the filtration process. All of the surfaces of the system which come in contact with the blood and fluids which are infused into the patient must be sterilized prior to commencing treatment.

Figure 1 illustrates a system for ultrapheresis. Blood is removed from a patient by means of a venous catheter **10** with the distal lead **11** thereof disposed in the superior vena cava **12** leading to the patient's heart **13**. The blood passes through conduit **14** to a drip chamber **15** and then into pump **16** which controls the pressure of the blood to the separation unit **17**, preferably an ultrafilter as shown, through conduit **18**. A pressure gauge **19** is provided on conduit **14** to continually monitor arterial pressure. A syringe pump **20** feeds an anti-clotting drug such as sodium heparin to conduit **18** to prevent the clotting of blood in the ultrafilter **17**. In the ultrafilter **17** the blood stream passes over the ultrafilter medium or membrane or absorbent column **21** under pressure. The blood fraction including the low molecular weight components passes through the membrane or absorbant column **21** and is discharged as permeate through conduit **22**. The retentate or treated blood containing the high molecular weight components, which include whole blood cells and platelets, is discharged into conduit **23** which ultimately leads back to

the patient. Volumetric pump **27** passes a controlled amount of permeate to a container **28** for containment and for measuring. Volumetric pump **30**, which is preferably the same type and capacity as pump **27**, pumps replacement fluid from a container **31** to conduit **32**, which directs the fluid to conduit **23** where it mixes with the retentate or treated blood. The treated blood and other components are returned to the patient through venous catheter **34**, the distal or discharge end of which is disposed in the brachiocephalic vein. The volumetric pumps **27** and **30** are preferably set either to pump the same total amount of fluid or to pump at the same rate, so that the same volume of fluid which is removed from the patient's blood stream as permeate is returned as replacement fluid. The blood stream in conduit **23** is passed through filter **36** to remove clots or other debris from the blood stream. A drip chamber **37** ensures that no significant quantities of air enter the patient's blood stream. A venous pressure gauge **38** is provided to continually monitor venous blood pressure.

Figure 2 illustrates another embodiment wherein blood removed from a patient is first passed through conduit **30** to a first ultrafilter **31** to selectively separate a blood fraction with components having molecular weights less than about 1,000,000 Daltons. The retentate from this ultrafiltration which contains the high molecular weight components is returned through conduit **32** to the patient. The permeate from the first ultrafilter **30** is passed through conduit **33** to a second ultrafilter **34** where a blood fraction having a molecular weight below 30,000 is removed from the permeate stream from the first ultrafilter **30**. The permeate from the second ultrafilter **34**, which contains the very low molecular weight components such as salts and nutrients may be returned to the patient through conduit [**38**] 35. The retentate from the second ultrafilter which contains blocking factors, IgG immunoglobulins and other components is discharged through conduit **36** and **13**.